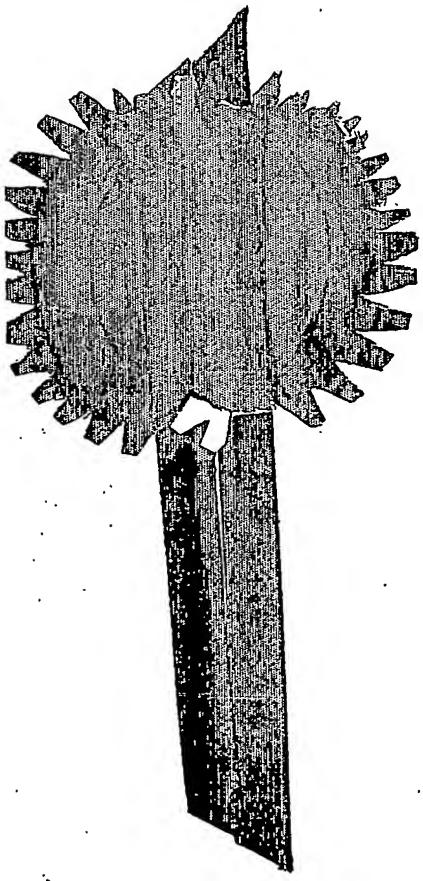
सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***859/Del/02*** *dated* ***23rd August 2002.***



Witness my hand this 29th Day of September 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5 (2), 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A METHOD FOR THE PREPARATION OF STABLE AQUEOUS SOLUTION OF RISPERIDONE"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. ASHISH GOGIA

b. SUNILENDU BHUSHAN ROY

c. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, ASHISH GOGIA, SUNILENDU BHUSHAN ROY, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon-122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(ASHISH GOGIA)

b.

(SUNILENDU BHUSHAN ROY)

c.

(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **683767** dated **06.08.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this 23RD day of **AUGUST, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

0850-2

23 AUG 2002

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

DUPLICATE

A METHOD FOR THE PREPARATION OF STABLE AQUEOUS SOLUTION OF RISPERIDONE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a method for the preparation of stable aqueous solution of risperidone for oral administration.

US Patent No. 4,804, 663 discloses an oral solution containing a 1,2-benzisoxazol-3-yl derivative, preservatives, tartaric acid, sodium-saccharin, flavors, and the polyhydric alcohols such as sorbitol and glycerol.

However, comparable solutions wherein the benzisoxazole derivative was risperidone, were found to exhibit an unsatisfactory physicochemical stability. And, sorbitol was found to cause decomposition of risperidone upon storage of the solution at elevated temperatures. A similar observation was made with the maltitol, suggesting that risperidone is incompatible with polyhydric alcohols.

Due to this incompatibility of risperidone with sorbitol, US Pat. Nos. 5,453,425 and 5,616,587 disclose an aqueous solution of risperidone essentially free of polyhydric alcohols such as mannitol, fructose, sucrose, maltose and the like.

Use of polyhydric alcohols, including sorbitol as a sweetener has many advantages, as these provide bulk and sweetness with a clean, cool pleasant taste. Sorbitol provides one-third fewer calories than sugar. It is an excellent humectant, texturizing and anti-crystallizing agent. Moreover Polyhydric alcohols are resistant to metabolism by oral bacteria, which break down sugars, and starches to release acids that may lead to cavities or erode tooth enamel. They are, therefore, non-cariogenic.

Sorbitol is slowly absorbed, therefore, when sorbitol is used, the rise in blood glucose and the insulin response associated with the ingestion of glucose is significantly reduced. Therefore Sorbitol can be used as an alternative to sugar for people with diabetes.

Moreover, Sorbitol has been affirmed as GRAS (Generally Recognized As Safe) by the U.S. Food and Drug Administration and is approved for use by the European Union and numerous countries around the world, including Australia, Canada and Japan.

Sorbitol is very stable, chemically inert and can withstand high temperatures. Moreover, the commercially available risperidone aqueous solution "Risperdal" needs to be diluted with 100ml of beverage before consuming. However polyhydric alcohol such as sorbitol, mannitol, fructose, sucrose, and maltose when used as bulk sweeteners give palatable aqueous solution, which can be administered as such without any dilution.

Hence, in view of the above advantages of polyhydric alcohols, it would be desirable to develop a method for stabilization of aqueous solution of risperidone containing polyhydric alcohols as sweeteners.

In the present invention, we have discovered that a stable aqueous solution of risperidone can be prepared even with polyhydric alcohols. By experimentation in our lab, we have discovered that a stable aqueous solution of risperidone containing polyhydric alcohols can be prepared by reducing the solid content and increasing the available water concentration of the aqueous solution. US Patent No. 4,804, 663 describes the aqueous solution of risperidone with less than 30% average available water content and solid content up to about 70%. However we found

that by reducing the solid content up to 10% and increasing the water content up to 90%, a stable aqueous solution of risperidone can be obtained. This solution was stable when kept for 4 weeks at a temperature of 80°C.

Further, it was discovered that addition of small amounts of antioxidant further improved the stability of aqueous solution without compromising on taste.

The present invention therefore provides a method for preparation of stable aqueous solution of risperidone comprising polyhydric alcohols as sweeteners.

It also provides a method for the preparation of stable aqueous solution of risperidone comprising polyhydric alcohols as sweeteners, wherein the solution further comprises stabilizing amount of antioxidants.

The solution prepared by the method of the present invention showed excellent stability and palatability and could be used without any further dilution.

The term "stable" as herein defined refers to a solution wherein, after storage for a period up to 4 weeks at a temperature of 80° C or below, the residual amount of risperidone is 80% or more of the initial risperidone concentration.

The term risperidone (3-[2-[4-(6-fluoro-1, 2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetr ahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one) as used herein comprises the free base form

and the pharmaceutically acceptable acid addition salts thereof. The amount of risperidone in the present compositions ranges from 0.01% to 1%.

The term polyhydric alcohols include monosaccharides such as glucose (dextrose), fructose (levulose); disaccharides such as sucrose, lactose, maltose, cellobiose; other sugars such as ribose, glycerine, sorbitol, xylitol, maltitol, erythritol, inositol, lactitol monohydrate, propylene glycol, galactose, mannose, xylose, rhamnose, glutaraldehyde, invert sugars, mannitol, polyethylene glycol, glycerol or mixtures thereof. The preferred sweeteners are sucrose and sorbitol that can be used in an amount of about 5 % to about 50% by weight of the total weight of solution.

The antioxidants for the present invention may be selected from any of the three classes of antioxidant i.e. true antioxidants, reducing agents and antioxidant synergist. The true antioxidants may be selected from the group consisting of acetylcysteine, alpha tocopherol acetate, d- alpha tocopherol, dl- alpha tocopherol, ascorbyl palmitate, butylated hydroxyanisole(BHA), butylated hydroxytoluene (BHT), cysteine, cysteine hydrochloride, propyl gallate and the like. The reducing agents may be selected from the group consisting of ascorbic acid, calicum ascorbate, calcium bisulphite, calcium sulphite, isoascorbic acid, potassium metabisulphite, sodium ascorbate, sodium bisulphite, sodium metabisulphite, sodium sulphite, sodium thiosulphate, thioglycerol and the like. The antioxidant synergists may be selected from the group consisting of citric acid, edetic acid (EDTA) and its salts such as disodium EDTA, hydroxyquinoline sulphate, phosphoric acid, sodium citrate, tartaric acid and the like.

Antioxidants, which are safe for ingestion and have sufficient solubility in the solution to make a stable single-phase composition, stable over a wide range of temperatures and pH values,

compatible with other components of the solution are preferred. Mixtures of two or more of the foregoing may also be used. The concentration of antioxidant may vary from about 0.01% to about 5.0% by weight of the total weight of solution.

The term "stabilizing amount" as used herein refers to an amount of antioxidants, which is sufficient to stabilize the risperidone solution.

Besides the above the oral solution of the present invention may also comprise of some other pharmaceutical additives such as antimicrobial preservatives, buffering agents, solubilizers, viscosity enhancing agents, colors, flavors and the like.

The preservatives of the present invention may be selected from benzoic acid, sorbic acid, methyl paraben or salts thereof, propyl paraben or salts thereof, benzyl alcohol and benzylalkonium chloride. The concentration of the preservatives may range from 0.05% to 2%.

Suitable solubilizer of the present invention may be a co-solvent, complexing agent, surfactant, wetting agent or the like.

Viscosity enhancing agents of the present invention may be selected from hydroxypropyl methylcellulose (some forms of which are available from Dow Chemical, Midland, Mich. USA under the METHOCEL trademark), hydroxpropyl cellulose and the like to provide a viscous mouth-feel similar to that of a traditional syrup.

Colors and flavors of the present invention may be selected from any FDA approved color or flavor suitable for oral use. Suitable flavoring substances are vanilla, cherry, raspberry, black currant, strawberry, Caramel Chocolate, Mint Cool, Fantasy flavors and the like. The total concentration of the flavoring substances may range from 0.01% to 2.0%.

The oral solutions according to the present invention have a pH from 2 to 6. The pH of the composition may be maintained by addition of buffers. Buffers may be selected from acid-base combinations such as succinic, tartaric, lactic, or citric acid with sodium hydroxide or disodium hydrogen phosphate.

The aqueous solution of the present invention may be prepared by:

(a) dissolving preservatives, stabilizers and acid component of the buffering system in hot purified water,

(b) followed by cooling;

(c) dissolving risperidone under continuous stirring in the solution of previous step

(d) followed by addition of sweetener

(e) adding colors and flavors; and

(f) adjusting pH with the basic component of the buffering system and making up the volume.

The following examples are intended to illustrate the scope of the present invention in all its aspects but not to limit it thereto.

Example 1

Ingredients	Quantity
Risperidone	1mg/ml
Benzoic Acid	1mg/ml
Tartaric Acid	7.5mg/ml
Sodium hydroxide	2 mg/ml
Sorbitol Solution (70%)	10%w/v
Artificial Creme De Vanilla Flavor	0.15%v/v
Artificial Raspberry Flavor	0.5% v/v
Purified water	q.s to 1 ml

Process:

1. Benzoic acid was dissolved in purified water at 60^0C.
2. Tartaric acid was dissolved in solution of step 1, followed by cooling to a temperature of less than 30^0C.
3. Risperidone was then dissolved into the above solution under continuous stirring.
4. Sorbitol solution (70%) was mixed with the bulk of step 3, proceeded by the addition of Artificial Creme De Vanilla Flavor and Artificial Raspberry Flavor.
5. The pH of the above solution of step 4 was then adjusted between 3-4 with sodium hydroxide solution, followed by volume makeup using purified water.
6. The bulk of step 5 was finally filtered through 5µm polypropylene filter and filled into suitable containers.

Example 2

Ingredients	Quantity
Risperidone	1mg/ml
Benzoic Acid	1mg/ml
Tartaric Acid	7.5mg/ml
Sodium hydroxide	2 mg/ml
Sorbitol Solution (70%)	10%w/v
EDTA disodium	1mg/ml
Artificial Creme De Vanilla Flavor	0.15%v/v
Artificial Raspberry Flavor	0.5% v/v
Purified water	q.s to 1 ml

Process:

1. Benzoic acid and EDTA disodium were dissolved in purified water at 60°C.
2. Tartaric acid was dissolved in solution of step 1, followed by cooling to a temperature of less than 30°C.
3. Risperidone was then dissolved into the above solution under continuous stirring.
4. Sorbitol solution (70%) was mixed with the bulk of step 3, proceeded by the addition of Artificial Creme De Vanilla Flavor and Artificial Raspberry Flavor.
5. The pH of the above solution of step 4 was then adjusted between 3-4 with sodium hydroxide solution, followed by volume makeup using purified water.
6. The bulk of step 5 was finally filtered through 5µm polypropylene filter and filled into suitable containers.

The above solutions when subjected to accelerated stability i.e. at a temperature of 80° C for a period up to 4 weeks, showed excellent stability. This is clearly evident from the data given in Table-1.

Table 1. Accelerated stability data generated at 80^0C for a period of four weeks

Formulation	**Risperidone concentration**	
	Initial	**After 4 weeks at 80°C**
Solution with 70% sorbitol	100%	<80%
Solution with 10% sorbitol	99.90%	88.60%
Solution with 10% sorbitol and EDTA di-sodium	102.50%	96.20%

WE CLAIM:

1. A method for the preparation of stable aqueous solution of risperidone for oral administration, comprising polyhydric alcohols as sweeteners.
2. The method according to claim 1 wherein the aqueous solution of risperidone further comprises a stabilizing amount of antioxidant.
3. The method according to claim 2 wherein the antioxidant may be selected from true antioxidants, reducing agents and antioxidant synergist.
4. The method according to claim 3 wherein the true antioxidants is selected from the group consisting of acetylcysteine, alpha tocopherol acetate, d- alpha tocopherol, dl- alpha tocopherol, ascorbyl palmitate, butylated hydroxyanisole(BHA), butylated hydroxytoluene (BHT), cysteine, cysteine hydrochloride, propyl gallate and the like.
5. The method according to claim 4 wherein the true antioxidant is cysteine.
6. The method according to claim 4 wherein the true antioxidant is cysteine hydrochloride.
7. The method according to claim 4 wherein the true antioxidant is butylated hydroxytoluene.
8. The method according to claim 4 wherein the true antioxidant is butylated hydroxyanisole.
9. The method according to claim 3 wherein the reducing agents is selected from the group consisting of ascorbic acid, calicum ascorbate, calcium bisulphite, calcium sulphite, ascorbic acid, isoascorbic acid, potassium metabisulphite, sodium ascorbate, sodium bisulphite, sodium metabisulphite, sodium sulphite, sodium thiosulphate, thioglycerol and the like.
10. The method according to claim 9 wherein the reducing agent is sodium metabisulphite.

11. The method according to claim 9 wherein the reducing agent is ascorbic acid.

12. The method according to claim 9 wherein the reducing agent is sodium ascorbate.

13. The method according to claim 3 wherein the antioxidant synergist is selected from the group consisting of citric acid, edetic acid (EDTA) and its salts, hydroxyquinoline sulphate, phosphoric acid, sodium citrate, tartaric acid and the like.

14. The method according to claim 13 wherein the antioxidant synergist is citric acid.

15. The method according to claim 13 wherein the antioxidant synergist is selected from edetic acid and its salts.

16. The method according to claim 15 wherein the edetic acid salt is disodium EDTA.

17. The method according to claim 13 wherein the antioxidant synergist is sodium citrate.

18. The method according to claim 13 wherein the antioxidant synergist is tartaric acid.

19. The method according to claim 2 wherein the antioxidant is present in the concentration of from about 0.01% to about 5.0% by weight of the total weight of solution.

20. The method according to claim 1 wherein the polyhydric alcohol is selected from the group consisting of monosaccharides, disaccharides and other sugars.

21. The method according to claim 20 wherein monosaccharide is glucose (dextrose) or fructose (levulose).

22. The method according to claim 20 wherein disaccharide is sucrose, lactose, maltose or cellobiose.

23. The method according to claim 22 wherein disaccharide is sucrose.

24. The method according to claim 20 wherein other sugars are ribose, glycerine, sorbitol, xylitol, maltitol, erythritol, inositol, lactitol monohydrate, propylene glycol, galactose,

mannose, xylose, rhamnose, glutaraldehyde, invert sugars, mannitol, polyethylene glycol and glycerol.

25. The method according to claim 24 wherein the other sugar is sorbitol.

26. The method according to claim 1 or 2 wherein the stable aqueous solution of risperidone further comprises of other pharmaceutical additives.

27. The method according to claim 26 wherein the other pharmaceutically acceptable additives are selected from the group consisting of preservatives, buffering agents, solubilizers, viscosity enhancing agents, colors, flavors and the like.

28. The method according to claim 27 wherein the preservative is selected from the group consisting of benzoic acid, sorbic acid, methyl paraben or salts thereof, propyl paraben or salts thereof, benzyl alcohol and benzylalkonium chloride.

29. The method according to claim 28 wherein the preservative is benzoic acid.

30. The method according to claim 27 wherein the buffering agents are acid-base combinations.

31. The method according to claim 30 wherein acid is succinic, tartaric, lactic, or citric acid and base is sodium hydroxide or disodium hydrogen phosphate.

32. The method according to claim 31 wherein the acid is tartaric acid and base is sodium hydroxide.

33. The method according to claim 27 wherein the flavors are selected from vanilla, cherry, raspberry, black currant, strawberry, Caramel Chocolate, Mint Cool and Fantasy flavors and combinations thereof.

34. The method according to claim 33 wherein the flavor is a combination of Vanilla and Raspberry.

35. A process for the preparation of stable aqueous solution of risperidone for oral administration, comprising polyhydric alcohol as sweetener, optionally with stabilizing amount of antioxidant and other pharmaceutically acceptable additives substantially as described and illustrated by the examples herein.

Dated this **23RD** day of **August, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)

Company Secretary